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REVIEWS

# Primary and Secondary Cardioneuropathies and Their Functional Significance

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**For most functions of the heart its nerves are as important as its coronary arteries, but this is particularly true concerning cardiac rhythm, conduction and repolarization. It is thus paradoxical that postmortem correlative studies of sudden death virtually always include careful scrutiny of the coronary arteries but only rarely of the cardiac nerves or ganglia. In this review, abnormalities of the cardiac nerves and ganglia, collectively termed cardioneuropathies, are examined from the dual standpoint of their structural appearance and functional significance. Some cardioneuropathies are found in the absence of any other significant structural abnormality detectable in the heart and these are designated as primary cardioneuropathies. A viral etiology or some heritable disorder must rank high among possible causes. Secondary cardioneuropathies are those observed in association with almost every disease that can affect the heart; examples include myocardial infarction, infections, amyloidosis and cancer, but there are many others.**

**Because abnormalities of the heart's nerves and ganglia not only have their own unstabilizing influence on cardiac electrical activity but can also profoundly alter a patient's responses to pharmacologic treatment, it is hoped that future clinicopathologic examinations will more often include their careful study and thereby add to our meager knowledge about these important structures.**

Many different systems and processes help to assure optimal performance of the human heart, and nearly all of these are phasic or cyclic in nature. Examples include energy production by myocytes, ion transport across their membranes, preservation of appropriate coronary flow and lymphatic drainage and, with every heartbeat, the coordinated and efficient events of myocardial contraction. But there is almost no system or process that is not directly or indirectly influenced by the cardiac nerves, usually profoundly. Physiologists and pharmacologists have long appreciated the importance of neural control of the heart, and clinicians are becoming increasingly aware of it. Much of the recent clinical interest has been stimulated by the availability of new forms of treatment. Physicians can now selectively block certain neural events, such as activity of the adrenergic beta-receptor, or cause the heart to function either partially or totally independent of neural influence by using electronic pacemakers or cardiac transplantation.

Cardiac pacing and transplantation of the heart have also been the source of some paradoxical disinterest in cardiac neural control, because it is clear that the heart can function reasonably well when thus dissociated from action by its nerves. However, none would argue that the paced or transplanted heart represents optimal circumstances. Furthermore, all other patients and every normal subject have a heart which is constantly under the influence of the autonomic nerves. This powerful influence is not only direct, but it also indirectly modifies the response by the heart to most cardiac medications and circulating ions, hormones and other naturally occurring substances. Finally, in addition to its responses to extracardiac neural influence, the heart also serves as the source of much sensory information that is neurally mediated (1).

## Cardioneuropathy

Given all the physiologic, pharmacologic and clinical reasons to know as much as possible about neural control of the heart, the lack of much information about the normal anatomy and pathologic changes that may occur within the heart's neural elements is disappointing. In contrast to the

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extensive and meticulous descriptions of the major coronary arteries that are routinely provided with every good necropsy examination, it is unusual to hear or read any comments about cardiac neural elements, although there are some commendable exceptions (2–5). Some of the disinterest by morphologists is historical in origin. For example, near the turn of the century furious debates raged over the question of whether electrical activity of the heart was fundamentally neurogenic or myogenic. Although every aspect of the electrical activity of the heart is indeed remarkably influenced by its nerves, it is now generally appreciated that the cells fundamentally responsible for such activity are all myocytes. Because of this emphasis on the muscle of the heart, study of its nerves began to be neglected and often still is.

One approach to better understanding of neural control of the heart is by more careful examination of cardiac neural elements during every necropsy. There are two reasons why the regions of the sinus node and the atrioventricular (AV) node or His bundle are particularly suitable for this purpose. First, these special regions are normally richly innervated in the human heart and contain both parasympathetic (vagal) and sympathetic neurons (6). Second, in known or probable disorders of cardiac electrical stability (for example, sudden unexpected death) these are the regions where neural disease (or its absence) may be particularly important.

For a number of years my own clinicopathologic correlative studies have dealt particularly with the system of impulse formation and conduction in the heart, and they have included careful examination of local nerves and ganglia. To encompass all abnormalities that may be found in any of these neural elements I suggested the term *cardioneuropathy* (7), which encompasses both nerves and ganglia and includes morphologic abnormalities as varied as fibrosis, edema, infection (or inflammation) and all stages of degeneration. There are a variety of etiologies for cardioneuropathies, most of which can be usefully divided into primary or secondary for the sake of discussion. As will quickly become apparent, however, there may be both primary and secondary causes of cardioneuropathy within the same heart. This is particularly true for those heritable neuromuscular disorders that are known to involve the heart, such as progressive muscular dystrophy (8) or Friedreich's ataxia (9).

**Primary versus secondary cardiomyopathy.** Although it can be logically suspected that the cardiac nerves participate in the widespread neurologic disease of patients having

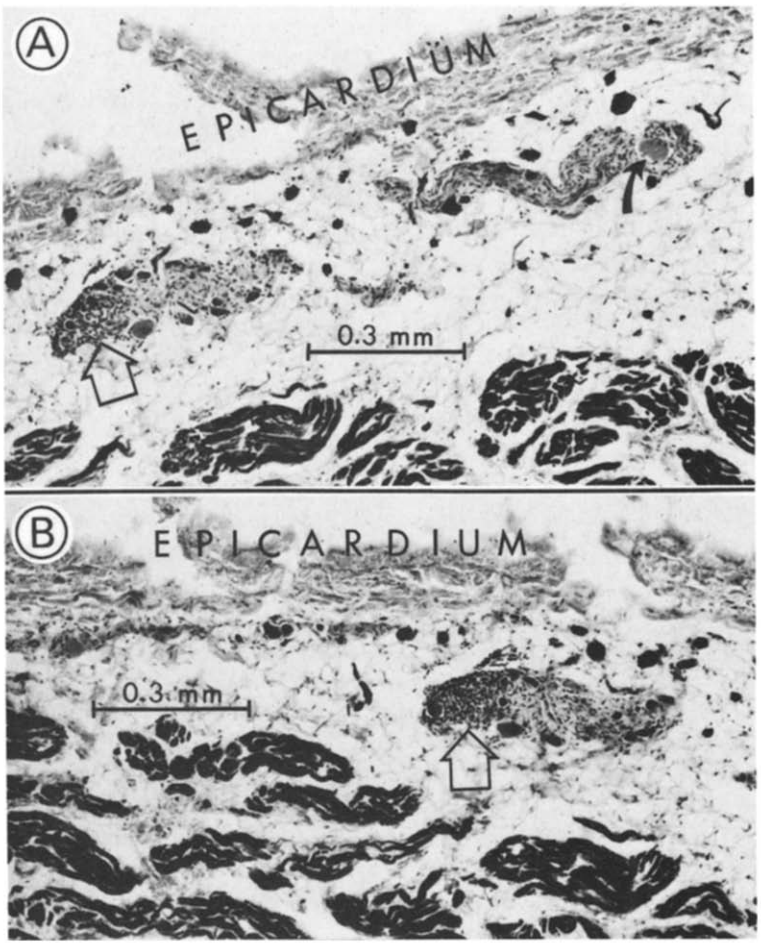


**Figure 1.** Ganglionitis near the sinus node illustrated in two photomicrographs from the heart of a young woman who was the victim of sudden unexpected death. **Open arrow** in **A** and **B** indicates a focus of inflammation present in two adjacent histologic sections. **Curved arrow** in **A** marks one swollen neuron. Goldner trichrome stain in this and all subsequent illustrations unless indicated otherwise. Magnification is represented by a reference bar.

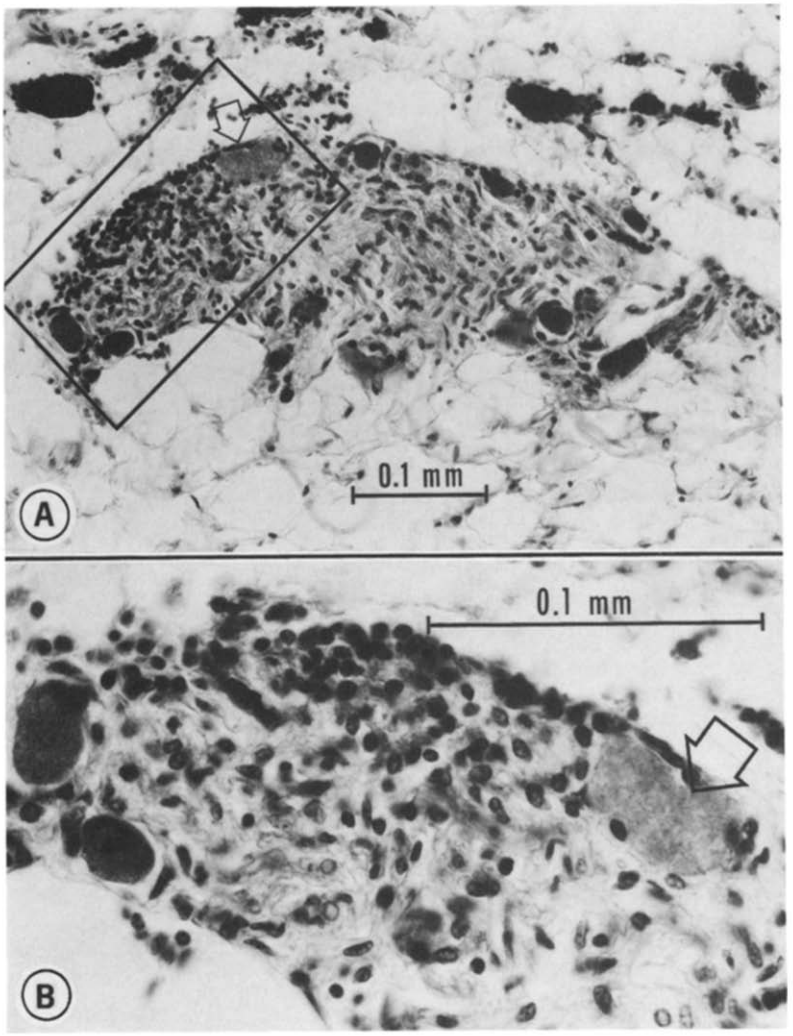


**Figure 2.** Same case as in Figure 1. Ganglionitis is shown here in more detail. Area boxed in **A** is shown in **B** at higher magnification. A swollen neuron is indicated by **open arrow**.

cardiomyopathy in association with certain heritable neuromuscular disorders, there is concomitantly an obliterative process of many small coronary arteries in these same patients (10). The arterial disease may in turn lead to ischemic damage of neurons along with any other underperfused structure in the heart. Whether the arterial disease itself may, on the contrary, be a secondary consequence of the cardioneuropathy is a separate and currently unanswered question. Two other examples of cardioneuropathy of probably mixed etiology include diabetes mellitus, where vascular and neural disease may compound each other but almost certainly have separate original pathogenesis, and diphtheritic cardioneuropathy, where the local infection or inflammation is compounded by the damage due to circulating neurotoxin (11).

Another factor that may confuse the definition of primary cardioneuropathy, even in diseases that are predominantly or exclusively neural in nature, is the fact that extracardiac neural destruction may be reflected by secondary intracardiac degeneration of the Wallerian type. This caveat applies both to heritable neuromuscular diseases and to those caused by neurotropic viruses. However, with these qualifications, heritable neurologic diseases (especially ones associated with cardiomyopathy) and viral infections may be the two best available examples of what may be designated as *primary cardioneuropathy*. Although there may be highly selective environmental or metabolic neurotoxins, too little is known about this possibility to merit its further discussion.

*Almost any disease that can cause damage within the heart may and usually does include its neural elements.* Examples include myocardial infarction, amyloidosis, sarcoidosis, bacterial infections such as tuberculosis or Whipple's disease, and cancer, but there are many other such diseases. Since important neural elements are found abundantly within or near the epicardium, pericarditis of any etiology will at least transiently be associated with cardioneuropathy. Because the original disease in all these ex-

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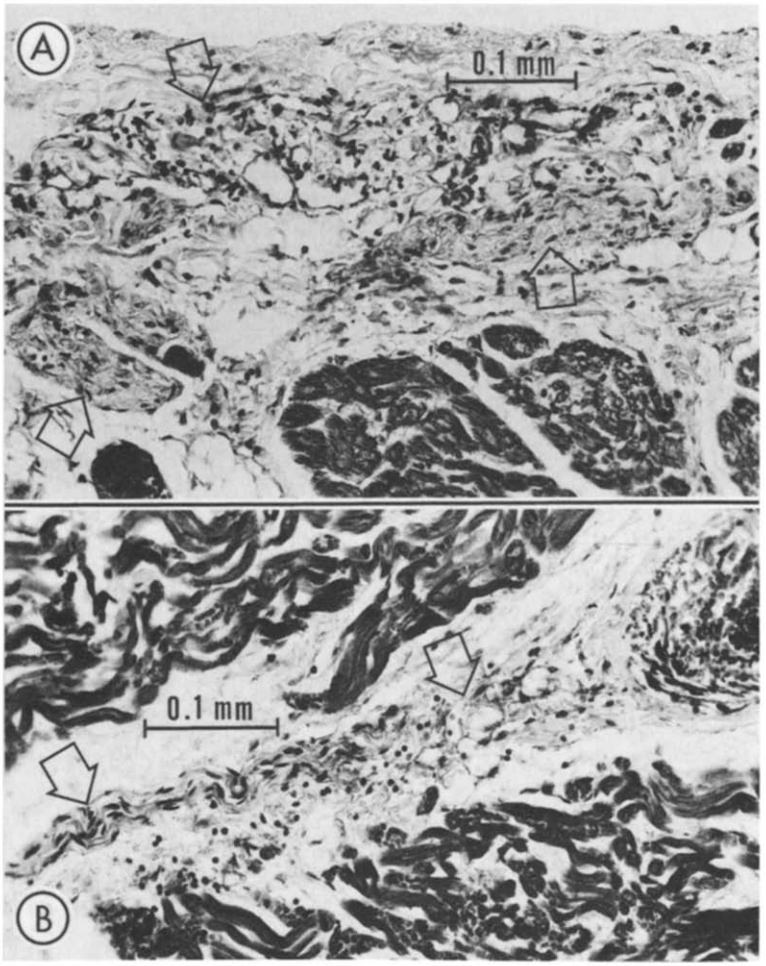


**Figure 3.** Inflammation and degeneration within nerves (**open arrows**) near the sinus node of a young man who died suddenly and unexpectedly. Nerve in **A** lies directly beneath the epicardium, while that in **B** is within the atrial myocardium. There was no inflammation except within and near the nerves.

amples is not primarily neural in nature, damage to cardiac neural elements associated with such diseases may be classified as *secondary cardioneuropathy*.

## Methods

**Pathologic material.** For the purpose of this review, archival material was examined to provide illustrative examples. Hearts restudied included ones from patients dying with amyloidosis (12), progressive muscular dystrophy (13), Friedreich's ataxia (9), Whipple's disease (14), pericarditis (15) and myocardial infarction (16), from diabetic individuals, from patients dying after cardiac surgery (17) and from patients with malignancies involving the heart (18,19). Other hearts reexamined included some from patients who died suddenly in association with the long QT syndromes (20) and some in which the only intracardiac abnormality was neuropathy (21,22). All of these and some additional similar hearts were from patients who died with documented arrhythmias or conduction disturbances, or both, and many were from patients whose death was both sudden and unexpected. Other details concerning this source material are available in the references just cited.

**Histology.** New histologic sections were cut and special stains were applied where appropriate. Methods within this laboratory for studying the system of impulse formation and conduction have been published previously (23,24). Photomicrographs were prepared to illustrate the histologic nature of primary and secondary cardioneuropathies.

*Although autonomic nerves and ganglia are abundant within the heart, they are not ubiquitous or homogeneously distributed.* Nerves, including the smaller branches, tend to course parallel to coronary arteries, and often form a paired flanking escort for small arteries viewed in cross section. By the nature of most of my histologic studies, multiple sections from the sinus node, AV node and His bundle are always examined. These sections permit an assessment of the pericardium seen over the sinus node, and of both the interatrial and interventricular septa routinely available in the multiple sections of the AV junction. In selected cases, tissue was also examined from the free wall of the right and left atria and both ventricles, and from the vicinity of the major coronary arteries. In every case, some tissue in the

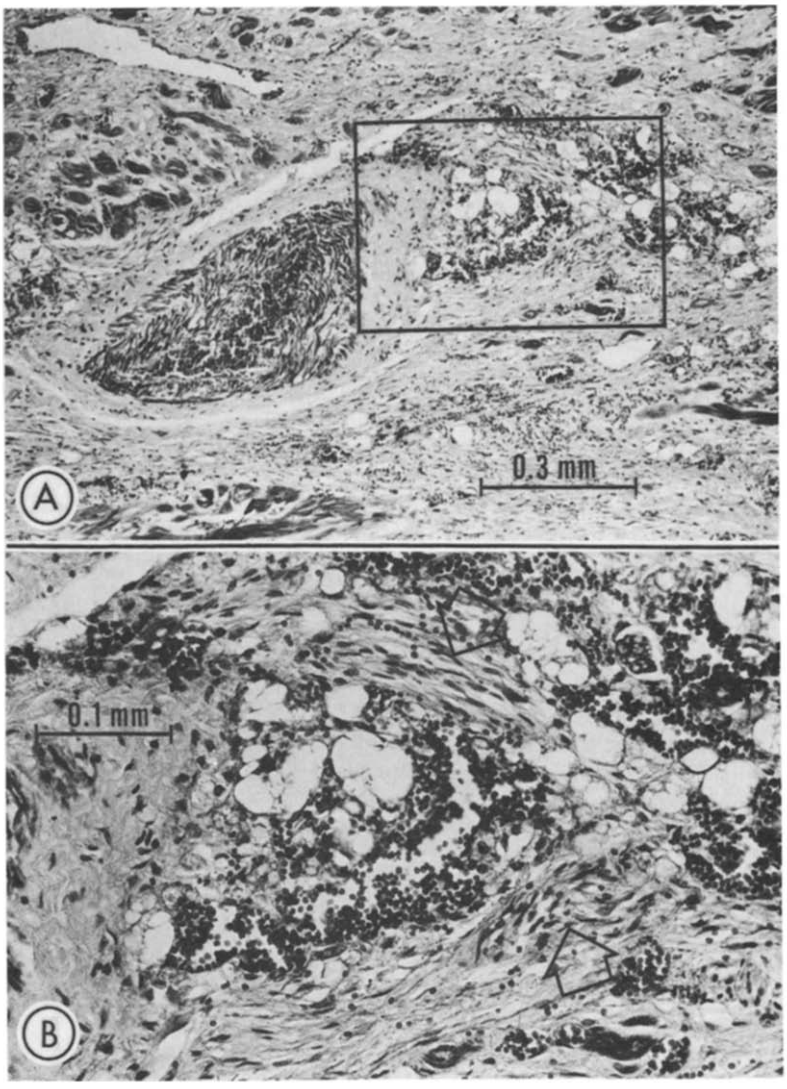


**Figure 4.** Right atrial cardioneuropathy from the heart of a young man with Friedreich's cardiomyopathy who had multiple atrial arrhythmias. Recognizable nerve is marked with **open arrows** in **B**, which is a higher magnification of the area boxed in **A**. Other examples from this same case are shown in Figure 5, 6 and 7.

vicinity of the root of the aorta was available in sections that were prepared for study of the distal His bundle and proximal bundle branches.

*Ganglia* are normally most abundant near the anterior and posterior margins of the sinus node, between the coronary sinus and AV node, throughout much of the interatrial septum, near the origin of the aorta and pulmonary artery and around the proximal portion of the main coronary arteries (6). Ganglia are rare within the sinus node itself, or within the AV node or His bundle, or within the ventricular myocardium. Based on classic physiologic concepts, ganglia found in the heart are nearly all thought to be vagal (parasympathetic). The cardiac sympathetic nerves are postganglionic.

*Certain enzymatic stains and ultrastructural features permit the differentiation of sympathetic from parasympathetic postganglionic nerves,* but most light microscopic characteristics do not permit such differentiation. In the vicinity of large coronary arteries, near the great vessels and occasionally near the epicardium elsewhere (for example, over the sinus node) one may see heavily myelinated nerves, but the majority of nerve profiles that are encountered are either thinly myelinated or unmyelinated.

*Certain special structures serve as probable neuroreceptors within the heart, and these have a variety of histologic appearances (1).* Additionally, much of the chemosensory and some of the pressosensory function in the heart is performed by small inconspicuous unmyelinated fibers diffusely distributed within the myocardium. These small nerves have no distinguishing histologic features recognizable with light microscopy. One particular neuroreceptor responsible for a cardiogenic hypertensive chemoreflex has been the subject of numerous studies from this laboratory (25,26); although preliminary examinations of it in association with cardiac disease have begun, it will not be the subject of further discussion here.

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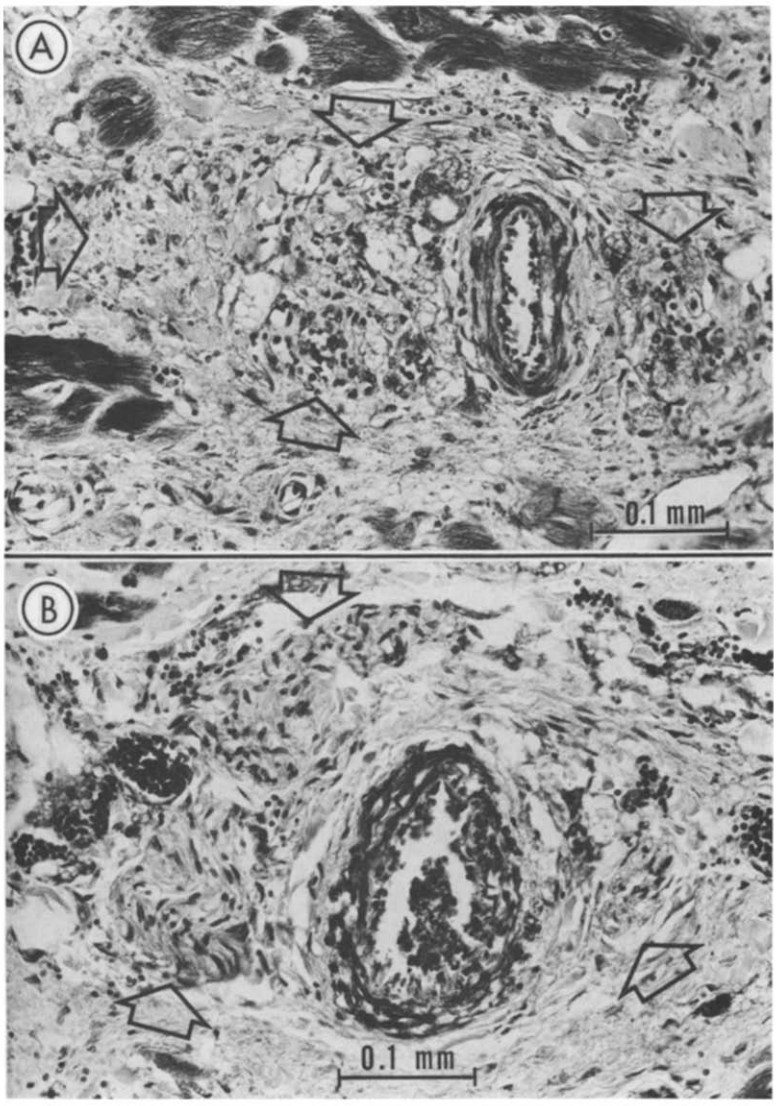


**Figure 5.** Same case as in Figure 4. Vesicular degeneration, fibrosis and inflammation are present in the nerves (**open arrows**) flanking two different small coronary arteries near the sinus node.

**Histologic stains and preparations.** For the present histologic studies of cardiac nerves and ganglia, a Goldner trichrome stain proved to be fully satisfactory and dependable in providing clear definition of these structures. When appropriate, the Gomori methenamine or Holmes silver impregnation, the Congo red (for amyloid), or periodic acid-Schiff stains were additionally employed. To assess minor or suggestive changes observed in any given nerve or ganglion, serial sections proved to be essential. As a result, for any region to be studied for neural elements, I now begin with at least 10 serial sections and more are prepared when indicated. This serial visualization permits accurate identification of neural elements, which on a single section may be so badly damaged by disease as to be unrecognizable. Furthermore, it allows one to assess not only the presence but also the extent of inflammation, damage or infiltration within an identified nerve or ganglion.

## Histologic Characteristics of Cardioneuropathy

**General description of nerves.** Damaged or injured nerves may be surrounded by inflammatory cells or, less often, permeated by them. These cells most often are predominantly lymphocytes, except in regions of overt myocardial necrosis. Where there is pericardial or epicardial fibrosis, nerves can also become entrapped and appear densely fibrotic or scarred. In addition, nerves are sometimes infiltrated by amyloid or malignant cells when these diseases exist in the heart. Less striking but important changes include vesicular disruption of nerve continuity and other distinct but nonspecific interruptions of the course of a nerve. Because so many cardiac nerves are normally unmyelinated, it is difficult to assess changes in myelin of the type known to be important in extracardiac neuropathology.

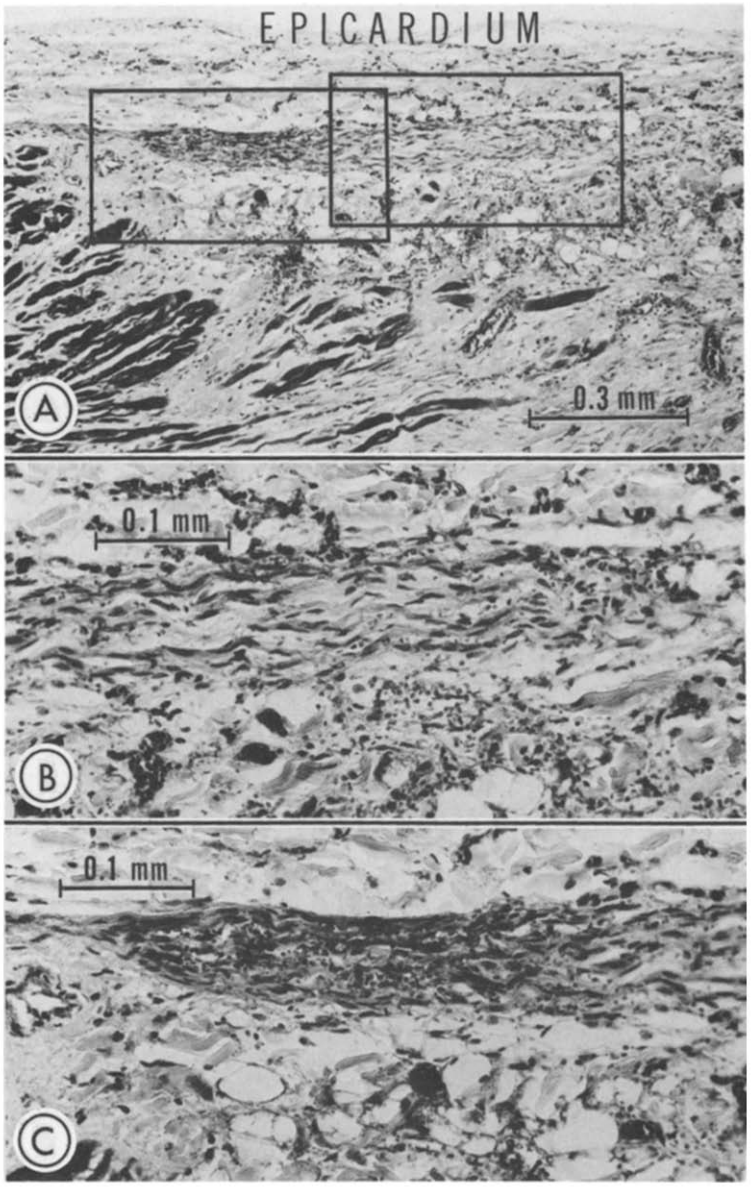


**Figure 6.** Same case as in Figure 4. Fragmentation and degeneration of a subepicardial nerve is depicted in **A**, with boxed areas seen at higher magnification in **B** and **C**. The pericardium is essentially normal.

**General description of ganglia.** Normal intracardiac ganglia vary widely in size and complexity, ranging from dozens of cell bodies to very small examples containing only one or two cells with their supporting structure. Inflammatory destruction of ganglia can be extensive, including dense infiltration with inflammatory cells. Infiltration of ganglia with amyloid or cancer can also be demonstrated and does not differ from the destruction similarly found in axons. An assortment of changes occur within multiple adjacent cell bodies of ganglia and these can be characterized by abnormal variegated staining (polychromasia), by either swelling or shrinkage (anisocytosis) and by changes in the normal consistency of cytoplasmic Nissl substance producing either coarsely granular clumping or homogenization with total loss of granularity.

**Examples of primary cardioneuropathy.** In some cases of sudden unexpected death (20–22), there are distinctive changes in neural elements of the heart (Fig. 1, 2 and 3). Because many of these hearts have had no significant abnormalities in the coronary arteries, no focal inflammation of the myocardium independent of the neural lesions and no significant pericarditis, the isolated cardioneuropathy may be deduced to be the primary fault. A viral infection must rank high among suspected causes, and virus-like particles have been demonstrated in the vicinity of such cardioneuropathy by special electron microscopic examination (27). However, much remains to be elucidated before one can conclude that these examples of primary cardioneuropathy are actually caused by a viral infection. Additional possible causes may include other types of infection, some environ-

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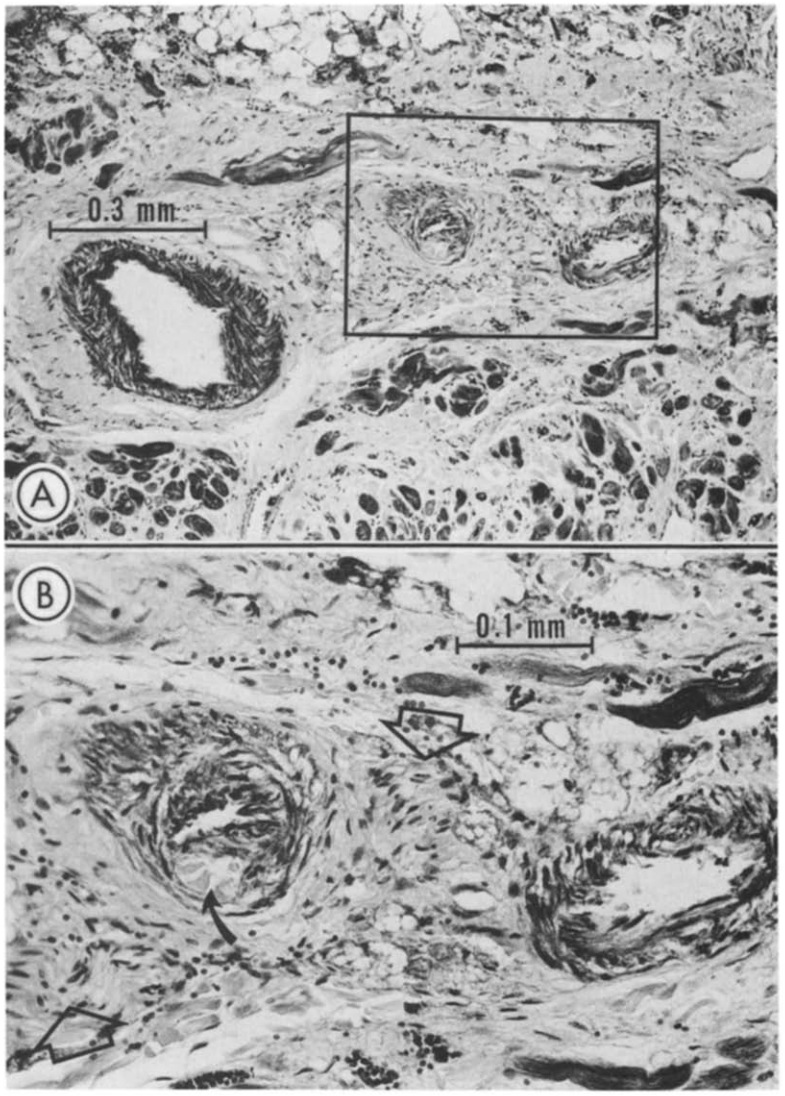


**Figure 7.** Same case as in Figure 4. Anatomic proximity of narrowed small coronary arteries (**curved arrow in B**) and degenerating nerves (**open arrows**) invite speculation as to their possible causal interrelation in Friedreich's cardiomyopathy, as discussed in text. Other areas of focal degeneration near the sinus node are seen near the top of **A**, above the area **boxed** for orientation to at higher magnification in **B**.

mental or endogenous neurotoxin or some specific nutritional deficiency, but the exact nature of any of these etiologies can, as yet, only be speculated on. QT prolongation has been documented in individuals who died suddenly while using a liquid protein diet (28), but the precise pathogenesis or causative relation is unclear.

*Heritable neuromuscular disorders such as progressive muscular dystrophy and Friedreich's ataxia are known to be associated with cardiomyopathy, and the heart muscle disease includes cardioneuropathy (8,9).* In some cases, the extent of neural damage is remarkable for its prevalance and its intensity (Fig. 4, 5 and 6). Because there are also associated narrowing lesions and degenerative changes within small coronary arteries (Fig. 7), it is difficult to know what the comparative temporal sequence of the neural and vascular lesions is. One faces the same dilemma concerning the pathogenesis of diabetic cardioneuropathy (Fig. 8 and 9). On the basis of our sparse present knowledge, it would be equally plausible to suspect that either caused the other. However, the focal lesions in segments of intracardiac nerves are not what one would expect secondary to distant (even extracardiac) neural disease causing Wallerian degeneration, which should cause more diffuse damage of the distal segment of nerve. Similarly, the presence of focal neural damage in regions where the local vessels are patent makes it less likely that the neural damage is ischemic in nature, although tedious histologic reconstruction would be necessary to eliminate that possibility. The more probable explanation, at least for now, is that both the nerves and the small arteries (and perhaps the myocardium itself) are the site of direct involvement by the original neuromuscular disease, but lesions in either system almost certainly compound or worsen those in the other.

**Examples of secondary cardioneuropathy.** Nothing is immutable in medicine, and it is possible that one day myocardial infarction or amyloidosis may prove to have an im-

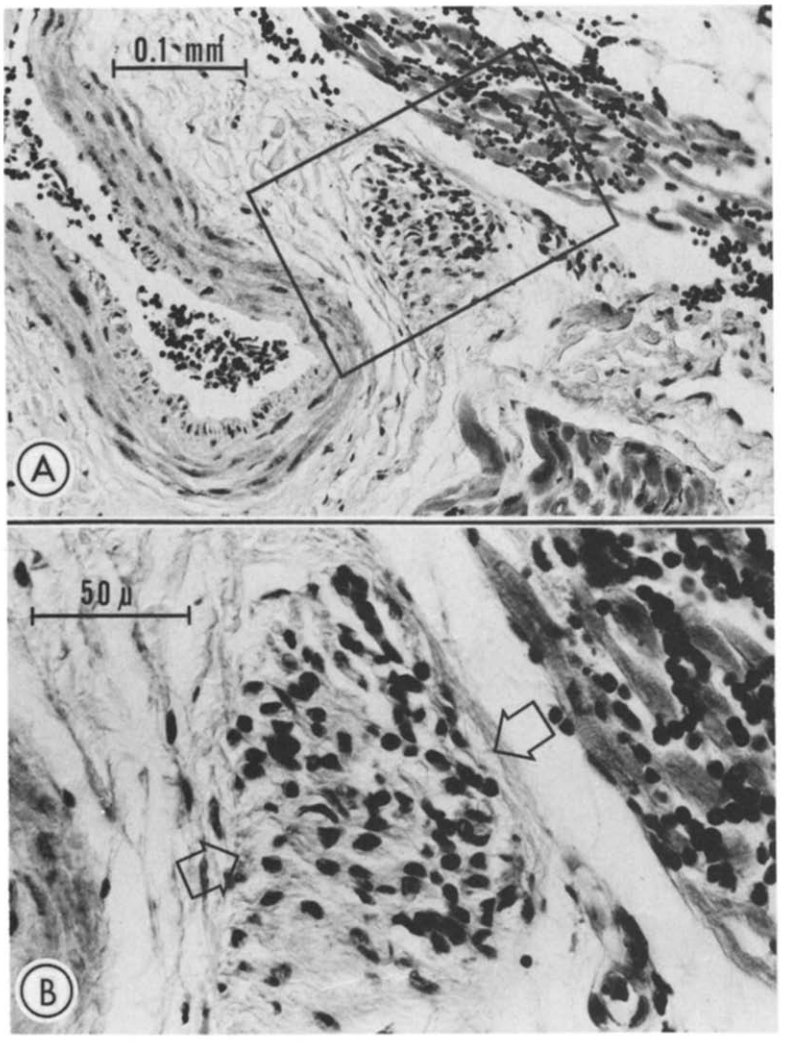


**Figure 8.** Inflammatory infiltration of a small nerve **boxed** in **A** (**arrows in B**) from the interventricular septum of a young woman with diabetes mellitus who died suddenly.

portant neural etiology. However, at present these two diseases may be considered as specific examples causing secondary cardioneuropathy. It has long been recognized that cardiac neural damage during myocardial ischemia and infarction (Fig. 10 and 11) contributes in an important way to the pathogenesis of arrhythmias and conduction disturbances (16,29,30). In addition to electrophysiologic sequences, one must also consider the possible influence of this type of cardioneuropathy on contractile properties of the heart, particularly dyskinesia and hypokinesia. Because cardiac nerves traversing an area of ischemic damage may also have distributed to a more distal nonischemic area, their disruption within the ischemic region may alter neural control outside that region (31). Finally, neural destruction may interrupt not only efferent but also afferent signals (32), depriving the infarcted heart of its ability either to respond to signals from or send signals through a particular nerve.

*As emphasized previously, virtually every cardiac disease will at least randomly—and for some, perhaps selectively—involve the nerves and ganglia of the heart.* Of many possible examples, two that illustrate this process are amyloidosis (Fig. 12) and the neural involvement by cardiomyopathy of Whipple's disease (Fig. 13). The clinical importance of any secondary cardioneuropathy may vary greatly, depending in part on what other problems are present. But to understand the pathogenesis of disturbances of cardiac rhythm or conduction and to plan their pharmacologic or other management in patients with such diseases, one must realize that cardioneuropathy can and does occur.

*After cardiac surgery, arrhythmias are sometimes a major problem.* There are numerous explanations for these postoperative arrhythmias, some examples being metabolic abnormalities (hypoxia, acidosis, electrolyte imbalance) and unavoidable direct injuries to the heart itself. That the surgery may cause neural damage is self-apparent, the incision transects nerves and sutures distort them (Fig. 14). There

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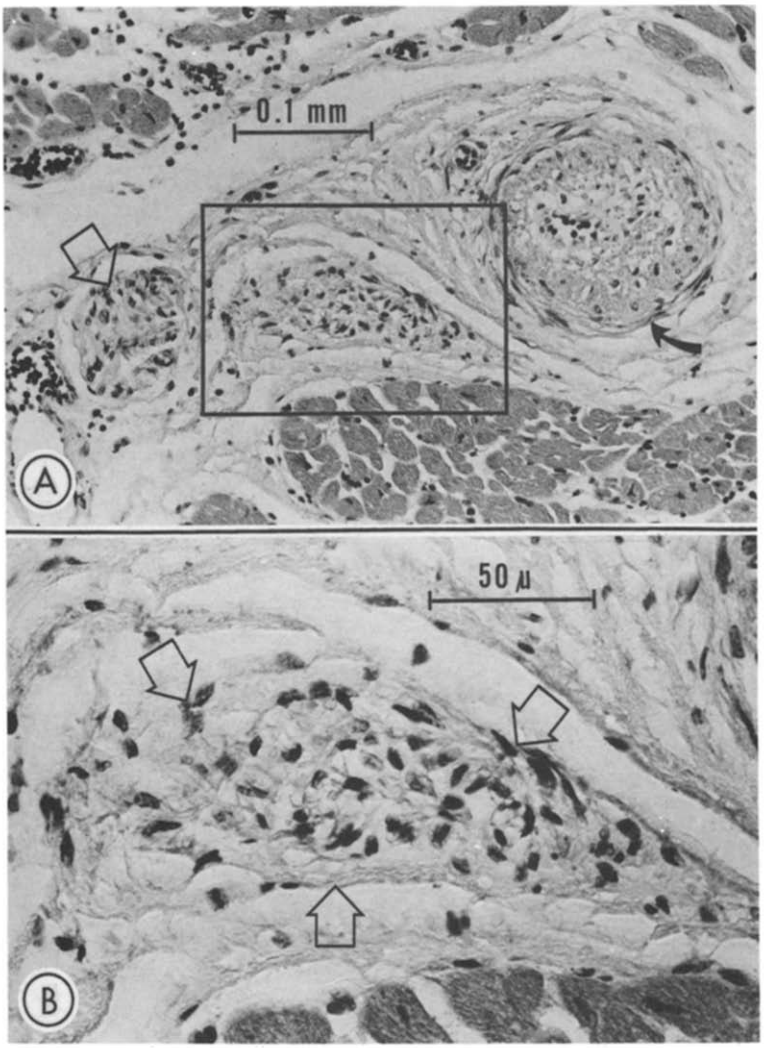


**Figure 9.** Same case as in Figure 8. In some places both the cardioneuropathy and coronary arteriopathy (**curved arrow in A**) are in direct proximity. Two nerve profiles are shown in **A**, one marked with an **open arrow** and the other **boxed** for depiction at higher magnification in **B** (**open arrows**).

may be no way to avoid such neural damage, but it is useful for understanding certain postoperative problems with cardiac rhythm to know that this form of secondary cardioneuropathy exists.

*Infiltrative malignant (usually metastatic) diseases of the heart are often associated with arrhythmias or other electrical disturbances.* There are multiple reasons why this occurs, including direct myocardial invasion and injury, coronary obstruction and damage within the conduction system itself (18,19). Also included is what happens to the cardiac nerves and ganglia (Fig. 15, 16 and 17). For a conceptual discussion of cardioneuropathies, the principal value of these illustrative examples is not the magnitude of their clinical importance in usually fatal diseases, in which a terminal arrhythmia can be a blessing in disguise, but to demonstrate the structural appearance of the neural lesions and determine from that what their functional significance may have been. They are thus, in essence, readily available examples of experiments of Nature.

## Functional Significance of Cardioneuropathies

Balance is so important in normal performance of the heart, whether the balance is for the integrity of its coronary circulation, the synchrony and effectiveness of myocardial contraction or the influence of its nerves and ganglia. Neural control of the heart is equally remarkable for its power and complexity. There are the two familiar directly opposing systems, the vagal and sympathetic. As new concepts of neurophysiology evolve, it will be necessary to add purinergic, dopaminergic, histaminergic, serotoninergic and probably other systems not easily fitted into adrenergic or cholinergic mechanisms in the classic sense, but those are beyond the scope of this discussion.

In addition to the influence of efferent neural signals to the heart, what may be considered its "motor" control but includes electrical and other functions, there is a growing appreciation of how the heart also functions as a sensory

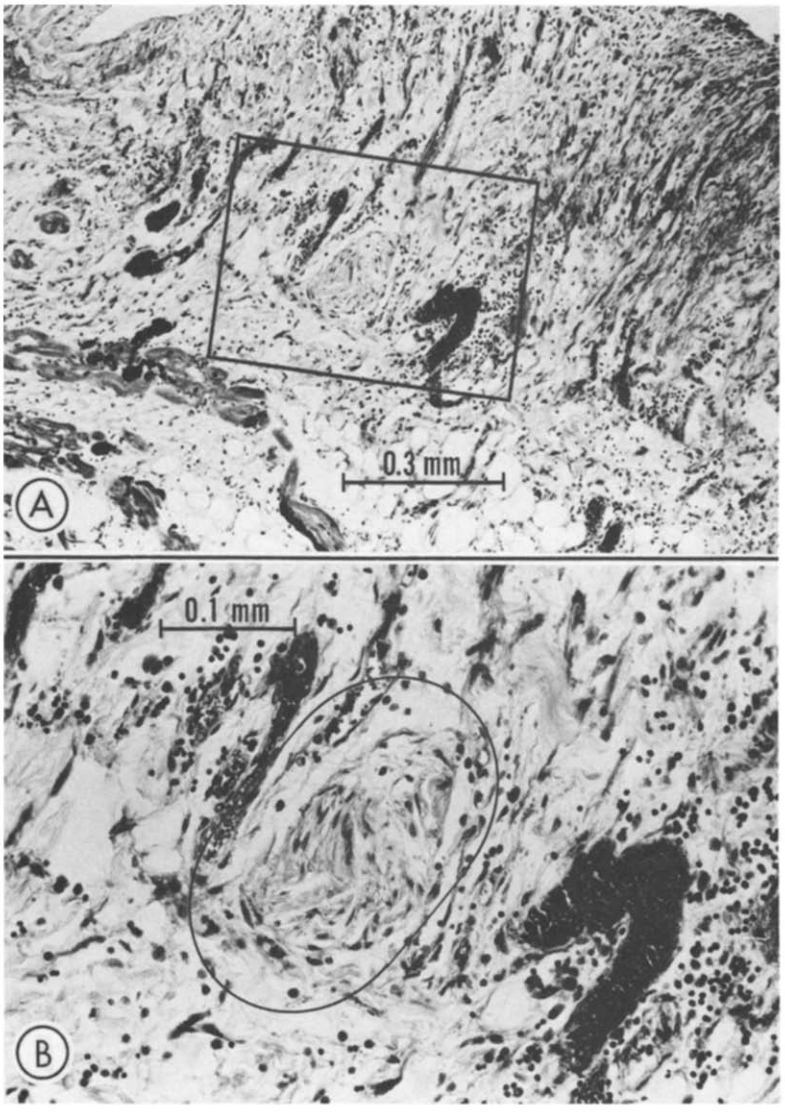


**Figure 10.** Cardiac nerves are not spared in the effects of myocardial infarction, shown here from the right atrium of a patient who died with atrial arrhythmias complicating a large posterior ventricular infarction. Area **boxed** in **A** contains one nerve, **circled** in **B**.

organ (1,25,26). Thus, the heart may be the source of neuroreflexes that influence not only its own function, but quite likely, the function of other organs in the body. Of course, normal performance by the heart is essential to the continued survival of all other organs, including many which are themselves the source of neuroreflexes that (to close the cycle) can alter cardiac performance.

**Cardiovascular reflexes mediated within the brain.** The brain unsurprisingly may be the most complex of these extracardiac organs that control the heart. It not only provides "tonic" regulatory influence from medullary and similar centers, but also mediates those thoughts and emotions that themselves have profound effects on cardiac performance. Finally, the brain is the place where all neuroreflexes are ultimately integrated, including those originating from or being directed toward the heart itself. There may be some exceptions where cardiospinal or cardiocardiac reflexes play a role, but these pale in comparison with the magnitude and wide array of cardiovascular reflexes mediated within the brain.

*Neural control of the coronary circulation includes its selective omission of response during some vasoconstrictive reflexes (33).* Although total cardiac denervation by autotransplantation of the heart has been advocated by some as a means of treating vasospastic angina (34), such treatment must be considered with special caution because other (nonneural) forms of coronary vasoconstriction have been documented in the transplanted human heart (35).

**Sinus node impulse and sinus node artery pulse.** In the special context of this review, there is an intriguing functional relation between pulse in the sinus node artery and impulse formation by the sinus node (36). This may at least partially be neurally mediated because the pulse-impulse relation can be abolished by beta-receptor blockade (37). There is, furthermore, no cholinesterase in the wall of the sinus node artery although this enzyme is abundant

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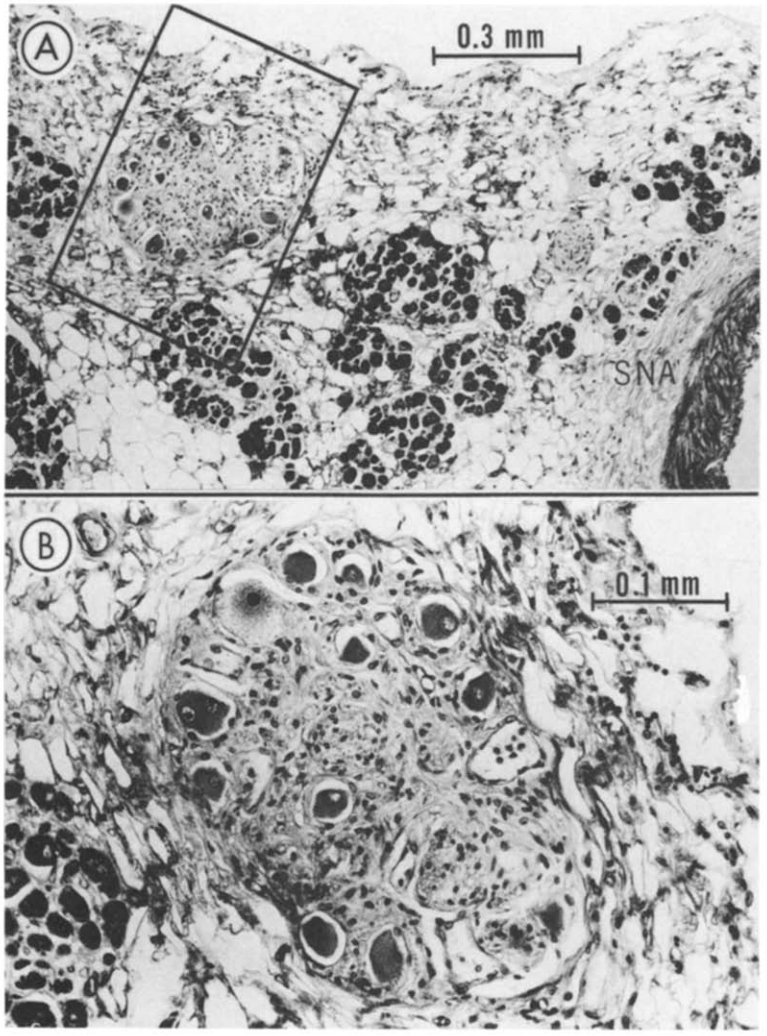


**Figure 11.** Degeneration within a ganglion near the sinus node of a second patient with acute myocardial infarction shown here at 2 magnifications. SNA is sinus node artery in **A**.

elsewhere in the sinus node (38), but it is not clear what the functional significance of this contrast may be.

**Neural control of contractility.** More familiar to most physicians are the studies of neural control of cardiac contractility, which can be profound indeed. In that context the power of positive inotropic influence by the sympathetic nerves on both the atria and the ventricles is indisputable, as is the negative inotropic influence by the vagi on the atria, but the magnitude of any inotropic effect by the vagi on the ventricles remains disputable and, in any event, must be small. Cardioneural effects on coronary circulation, myocardial contraction and certain other functions of the heart are all very important, but my own work has dealt more with cardiac electrical properties, which will be the subject of most of the subsequent discussion.

## *Cardiac Electrical Properties*

Every electrical property of the heart is normally under the continuing control of its autonomic nerves. This includes normal impulse formation, temporal and geometric dispersion of refractory periods and their duration both in the atria and ventricles, atrioventricular (AV) conduction, the rate and site of ectopic impulse formation, the onset and perpetuation of certain arrhythmias (notably atrial fibrillation) and myocardial repolarization. To illustrate the multifaceted nature of autonomic neural control, consider that the rate of the sinus node may be slowed either by vagal stimulation, adrenergic withdrawal, beta-receptor blockade or alpha-receptor stimulation (39). Conversely, sinus acceleration can be the result of sympathetic stimulation or of vagal withdrawal or blockade (40). In addition, neural facilitation or impairment can occur as the consequence of changes in the local concentration of potassium or calcium ion (among others) or of the humoral delivery of hormones or cardioactive medications, many of which have multiple other effects as well. Furthermore, there is growing appreciation of the dynamic control of the number and density of cellular receptors for neurotransmitters in many different diseases.

**Reflex heart block.** For some electrophysiologic responses by the heart, a cardioneuropathy may produce what

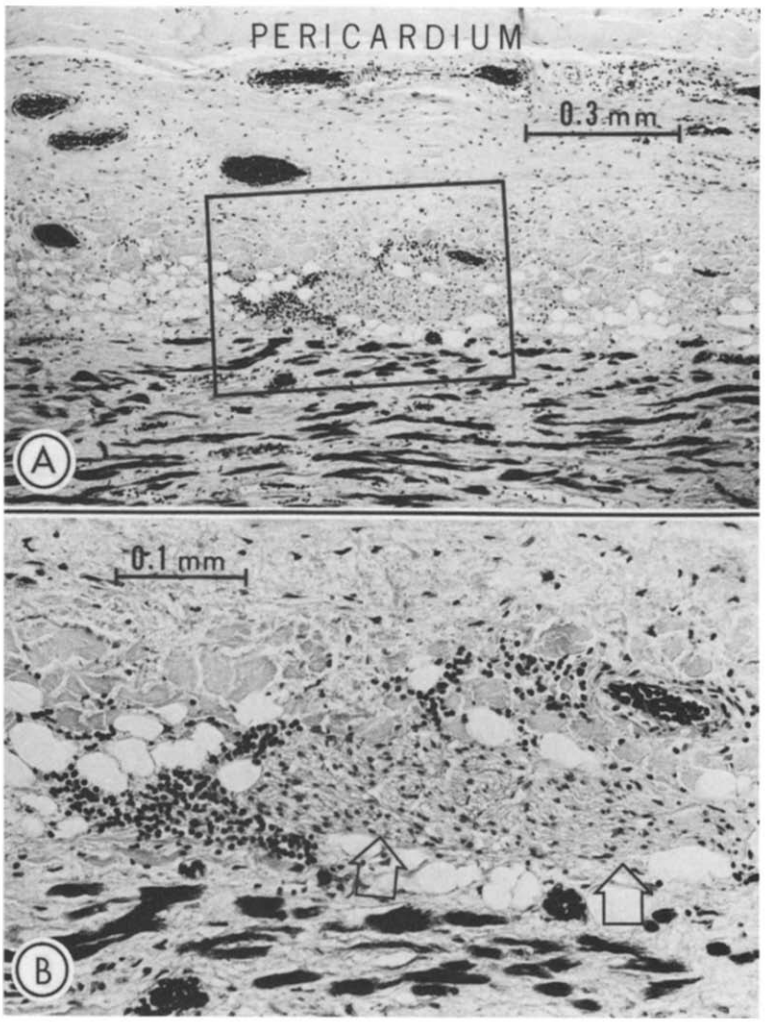


**Figure 12.** A right atrial nerve (**boxed in A**) is shown entrapped in the extensive subepicardial fibrosis present in the heart of a patient who died of cardiac amyloidosis. At higher magnification in **B** one sees focal inflammation around the nerve (**arrows**), and nearby deposits of amyloid recognizable by their waxy appearance.

at first seems a paradox. If local neural destruction makes the sinus node unresponsive to vagal influence, as is known to occur in diabetes (41) and with increasing age (42), then the vagal reflex effect can be heart block even though the AV node is functionally normal in all respects (particularly including its neural responsiveness). This type of "abnormality" of AV conduction is readily demonstrable experimentally by selective local perfusion of the canine sinus node with only a few micrograms of atropine and then observing the occurrence of transient heart block during the Hering-Breuer reflex, the Marey reflex or the cardiogenic hypertensive chemoreflex (43).

**AV junctional escape rhythms.** Escape rhythms also come under the influence of the cardiac nerves and will presumably be affected by cardioneuropathy when it is appropriately located. My colleagues and I have been especially concerned with two types of AV junctional escape rhythms readily demonstrable in the dog (44,45) and probably existing in human beings as well (46,47). We designated these as AVJ-1 and AVJ-2 rhythms. AVJ-1 rhythm (44) regularly emerges if the sinus node is selectively suppressed, although AVJ-2 rhythm (45) is seen to escape during maximal cholinergic suppression of the AV junction, which is heralded initially by the establishment of complete AV block. Although both of these AV junctional escape rhythms probably originate within the distal AV node near its junction with the His bundle (48,49), they differ from each other in two important ways. The first difference is mathematical. Stable AVJ-1 rhythm is consistently 66% of the control sinus rate (SR) although AVJ-2 is 22%, consequently being one-third of the rate of AVJ-1. Thus, the stable rates of these three rhythms form the ratio:

$$\text{SR: AVJ-1 : AVJ-2} = 9 : 6 : 2.$$

*The second difference between AVJ-1 and AVJ-2 rhythms is their autonomic neural responsiveness.* That of AVJ-1 is both qualitatively and quantitatively similar to that of the sinus node, whereas AVJ-2 can be accelerated by sympathetic influences but cannot be suppressed at all by acetylcholine. For any possible extrapolation of these experimental observations to normal or abnormal cardiac rhythms in human beings, it is essential to keep in mind that AVJ-1 and AVJ-2 rhythms have highly predictable rates only in

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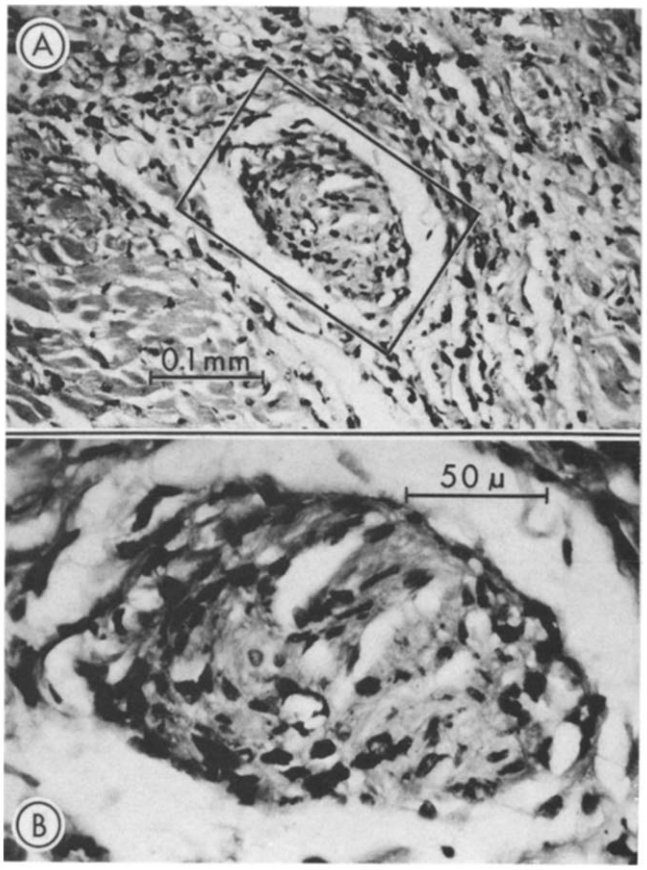


**Figure 13.** Whipple bacilli are seen as dark-staining structures, often in clumps, here in the right atrium of a patient with Whipple's cardiomyopathy. Area **boxed** in **A** is a nerve seen at higher magnification in **B**, filled with bacilli. Periodic acid-Schiff stain.

*normal* animals under *stable* conditions. Neither of these circumstances can be presumed to be true in most human examples. Arrhythmias in human beings most often occur in the presence of disease or malfunction in either the normal pacemaker (sinus node) or elsewhere in the heart, in the presence of medications that themselves influence electrical properties of the heart or in the presence of more general pathologic influences, including those mediated by autonomic nerves.

**Role of adrenergic neural influences on sinus and AV node junction.** Stable escape rhythms in the dog emerge predominantly from the AV junction, as discussed, although transient and erratic or unstable rhythms may emerge from other sites (50). If adrenergic neural influence within the AV junction of the dog is selectively eliminated by appropriate neural ablation or selective local administration of a neuronal blocking agent (guanethidine) or beta-receptor blocker (propranolol), then selective suppression of the sinus node is followed by long periods of cardiac standstill and eventually only the erratic and reluctant emergence of an AV junctional escape rhythm (51). Thus, although both the sinus node and the AV junction are demonstrably dependent on continued normal adrenergic neural influence, the AV junction is much more dependent than is the sinus node. In the presence of other depressant influences on AV junctional automaticity, such as those produced by "slow channel" or calcium blocking agents (verapamil, nifedipine), adrenergic neural influence is even more important for AV junctional escape to occur if the sinus node defaults (52,53).

**Drug-induced arrhythmias.** Even the arrhythmias caused by cardiac drugs such as digitalis or quinidine include in their mechanism certain important components of autonomic neural influence (54–57). In fact, the experimentally-produced "ventricular" arrhythmia of digitalis in the anesthetized dog can be terminated by the selective administration of either acetylcholine or neostigmine into the AV node artery (55). Whether this is to be interpreted that an acetylcholine-sensitive component of the AV junction is essential to the digitalis arrhythmia or not, it casts doubt on the frequently postulated role of Purkinje cell automaticity in the genesis of these and possibly other "ventricular" arrhythmias.

**AV conduction.** That AV conduction may be slowed or even interrupted by strong vagal influence can readily be demonstrated either experimentally or clinically. Every experienced cardiologist has witnessed transient heart block in some patients during carotid sinus pressure, especially on the left side. Whether sympathetic stimulation can actually accelerate AV conduction is less certain, however, for two reasons: 1) it is very difficult to separate direct sympathetic influence on conduction from its vagal-opposing effect, and 2) the frequent emergence of an AV junctional rhythm during sympathetic stimulation usually confuses the question of what is happening with local conduction.

**Neural control of repolarization (prolonged QT syndromes).** Repolarization, the last electrical event in the normal cardiac cycle, is remarkably influenced by both the vagal and sympathetic nerves. The clinical importance of this effect cannot be overestimated. For the vagus, the more prominent influence is within the atria (58), although the sympathetic influence there is comparatively less important. In the ventricles, the situation is just the opposite and the sympathetic influence is the more important. From the fundamental studies of Abildskov (59), it is now widely appreciated that asymmetry of sympathetic neural influence on ventricular repolarization is a major contributing factor in the pathogenesis of many types of ventricular arrhythmias. Examples include those occurring in individuals with bizarre QT prolongation in the electrocardiogram seen both in congenitally deaf and in normally hearing individuals, sometimes even in the same family (60). Consequently, it is of particular interest to this discussion that cardioneuropathy is present in the hearts of subjects dying with these long QT syndromes (20).

**Viral etiology for long QT syndrome?** Even though hereditary transmission of long QT syndromes has been repeatedly postulated as either autosomal recessive (in the

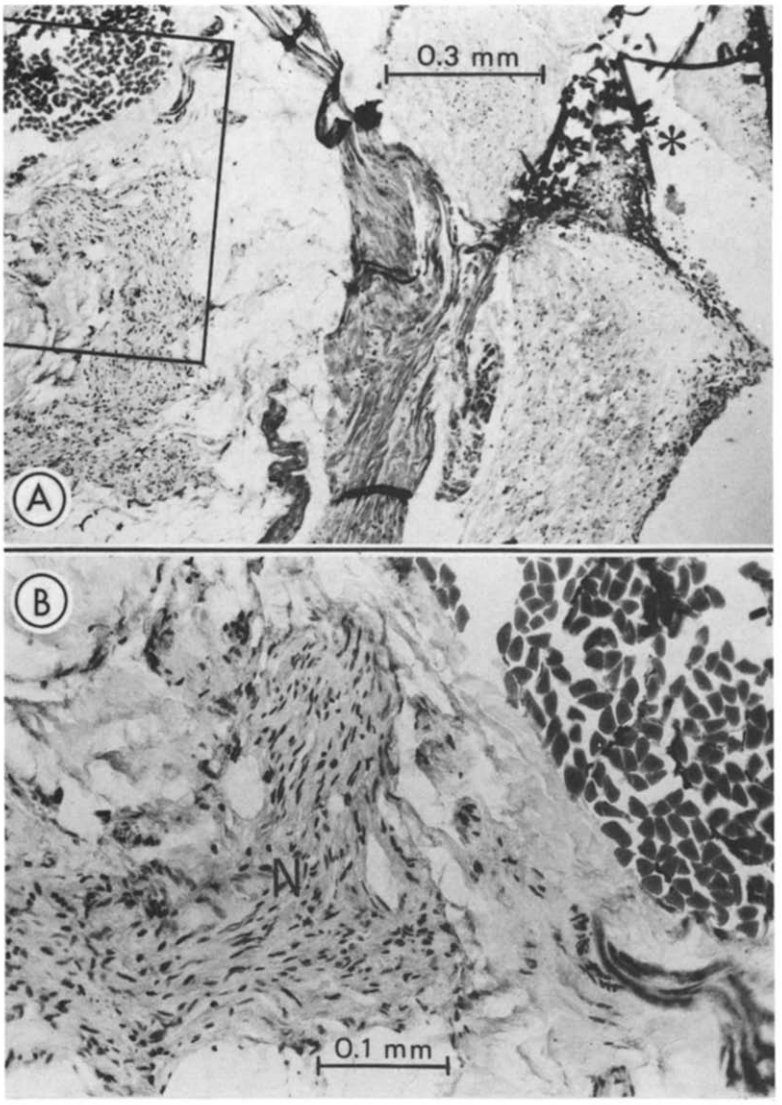


**Figure 14.** Sections are from the sinus node of a patient dying postoperatively. The incision necessary for surgical atriotomy will unavoidably transect or damage some neural elements. The incision in this heart is marked with an **asterisk** in **A** where some suture filaments are visible. More suture is seen directly adjacent to a nerve **boxed** in **A** and shown (marked **N**) at higher magnification in **B**.

deaf) or autosomal dominant (in those hearing normally), such hypotheses are difficult to reconcile with the observation that either deaf or normally hearing victims may be found within the same family. Because of that and the discovery of the cardioneuropathy, I suggested that the fundamental problem may be a shared familial infection such as a neurotropic slow virus (21,22,61). This hypothesis deserves further investigation for at least one particular clinical reason. If the pathogenesis of the cardioneuropathy among individuals with the long QT syndromes is, in truth, a chronic viral infection, which may be anticipated to vary in its intensity and expression just as infections with the varicella-zoster virus, for example, are known to do, then some of the postulated treatments such as stellate ganglionectomy could be temporarily beneficial but eventually dangerous. The adrenergic neural asymmetry, which might today be temporarily alleviated by surgically "balancing" the sympathetic neural influence on the heart, may tomorrow or later return when the cardioneuropathy progresses or worsens. Under those circumstances the enduring effect of stellectomy might even compound the adrenergic neural asymmetry, aggravate the electrical instability and increase the likelihood of sudden death.

## Discussion

**Pathogenesis.** Cardioneuropathy is a complex subject, whether examined from the standpoint of its pathogenesis, its functional significance or attempts at experimental investigation of either of these. Cancerous cardioneuropathy illustrates this complexity. When cancer metastasizes to the heart, the development of electrical instability is one of the earliest and most reliable clinical clues (62). Some of the explanation for this lies in the direct involvement of crucial

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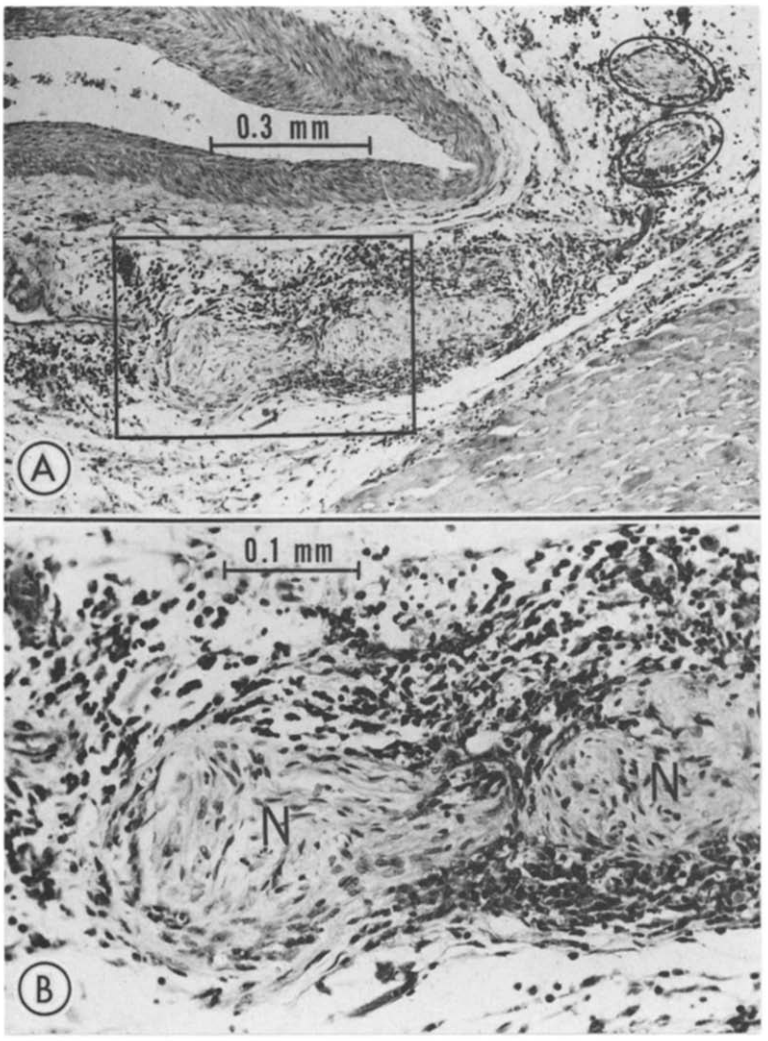


**Figure 15.** The cardioneuropathy shown here and in Figure 16 is from the left ventricle of a man dying with cardiac involvement by both lymphocytic leukemia and bronchogenic carcinoma. Ventricular arrhythmias were a major clinical problem. Two small nerves with surrounding malignancy are **circled** in **A**, and a larger nerve is **boxed** and shown at higher magnification in **B**.

sites within the heart by tumor, including actual invasion of nerves (Fig. 15 and 16), but there are several other important components in the pathogenesis of cardioneuropathy in association with cancer. Paraneoplastic neuropathy may produce major gastrointestinal dysfunction without tumor invasion of local autonomic nerves (63). Although the pathogenesis of this type of autonomic neuropathy is poorly understood, there is some experimental evidence that it may be mediated by a humoral factor (64). Furthermore, several forms of treatment such as irradiation and chemotherapy have their own independent neurotoxic influences, as may the malnutrition or generalized toxicity often found in patients with advanced forms of cancer.

*Even with more straightforward cardiac problems such as acute myocardial infarction or congestive failure,* there are obfuscating questions concerning neural control and response of the heart. Damage to neural elements during acute myocardial infarction unquestionably occurs (Fig. 10 and 11), but in the immediate recovery period there is a remarkable blunting of autonomic neural responses, such as the expected changes in heart rate during a simple Valsalva maneuver (65). This temporary blunting of chronotropic response persists for 1 to 2 weeks in patients with a small infarct and a well preserved ejection fraction, and for as long as 4 weeks in those with a larger infarct and a low ejection fraction. The chronotropic "incompetence" seems to be independent of the site of infarction, making injury to the sinus node (or its nerves) an improbable explanation. It is uncertain whether it may be due to a downregulation of adrenergic beta-receptor sites as has been demonstrated in patients with congestive heart failure (66). If it is due to a reduced number or density of such cellular receptors on myocytes, it is unclear how the change is produced or mediated.

*In diabetes mellitus* it has already been indicated that the cardioneuropathy may be a primary independent manifestation of the disease, or due to focal ischemia caused by the familiar associated coronary occlusive disease or possibly the consequence of some metabolic fault; most likely it is a combination of these. With the intriguing new evidence

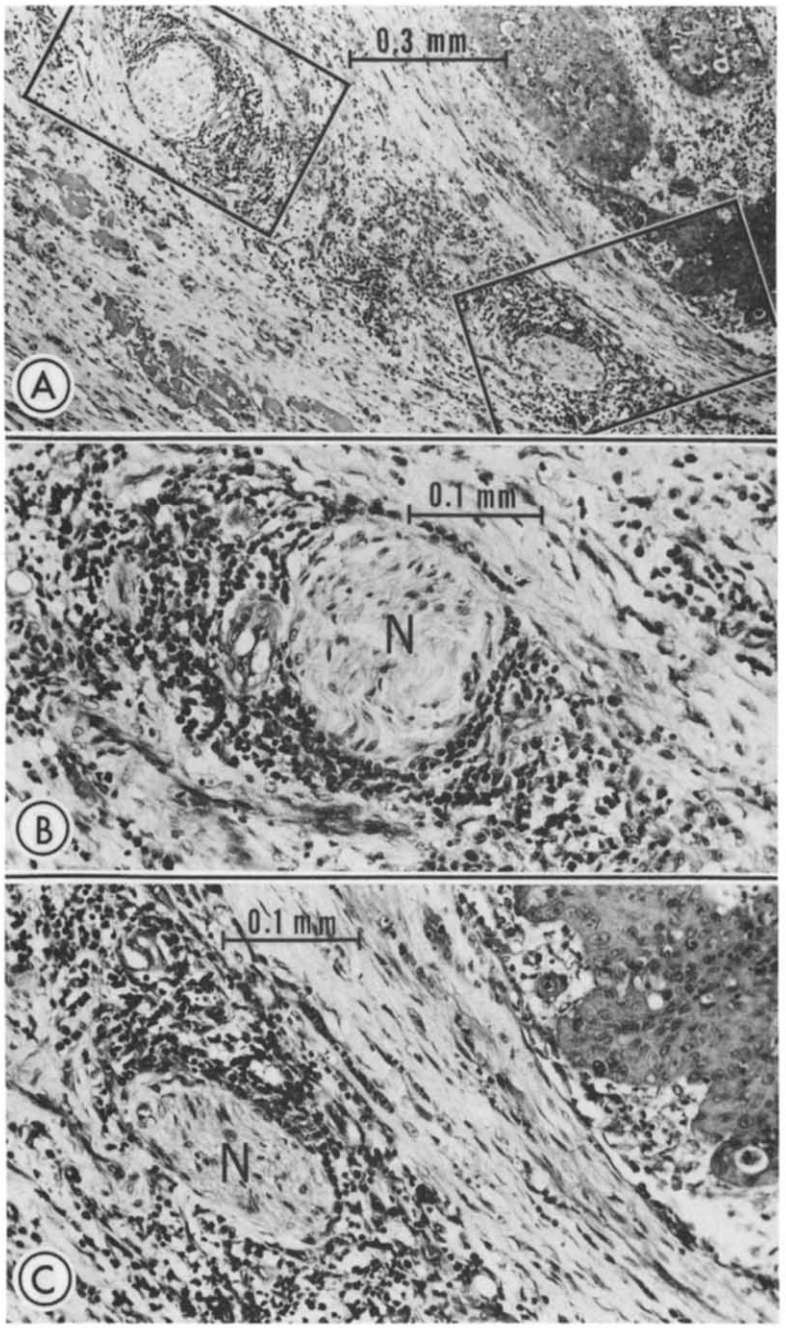


**Figure 16.** Same case as in Figure 15. Other examples of the cardioneuropathy and the histologic appearance of the dual malignancy are shown here. Tumor fills a major coronary artery in the **right upper third** of **A** and **right half** of **C**. Areas **boxed** in **A** are presented at higher magnification in **B** and **C**, with nerves marked **N**.

(67) that viruses may be responsible for some forms of diabetes in human subjects, it must be considered that these same viruses may cause direct damage to autonomic nerves, including those coursing to or normally residing within the heart.

*For most of us residing in the United States our experience with Chagas' disease is limited,* but this trypanosomal infection has a remarkable affinity for autonomic neural elements, particularly those in the heart (4). In certain countries of South America and less so elsewhere in the world, chagasic cardioneuropathy is a major public health problem very often heralded by disturbances in cardiac electrical activity. Much rarer but comparably important cardioneuropathy may occur in leprosy (68), a disease in which the structural damage of nerves has long been recognized as a major basis for physical deformity and disability.

**Ability of neural tissue to recover and regenerate.** Having reviewed the nature and significance of primary and secondary cardioneuropathies, it is fitting to conclude by calling attention to the remarkable but unpredictable ability of neural tissue to recover and regenerate. Visible histologic evidence of cardioneuropathy does not necessarily mean

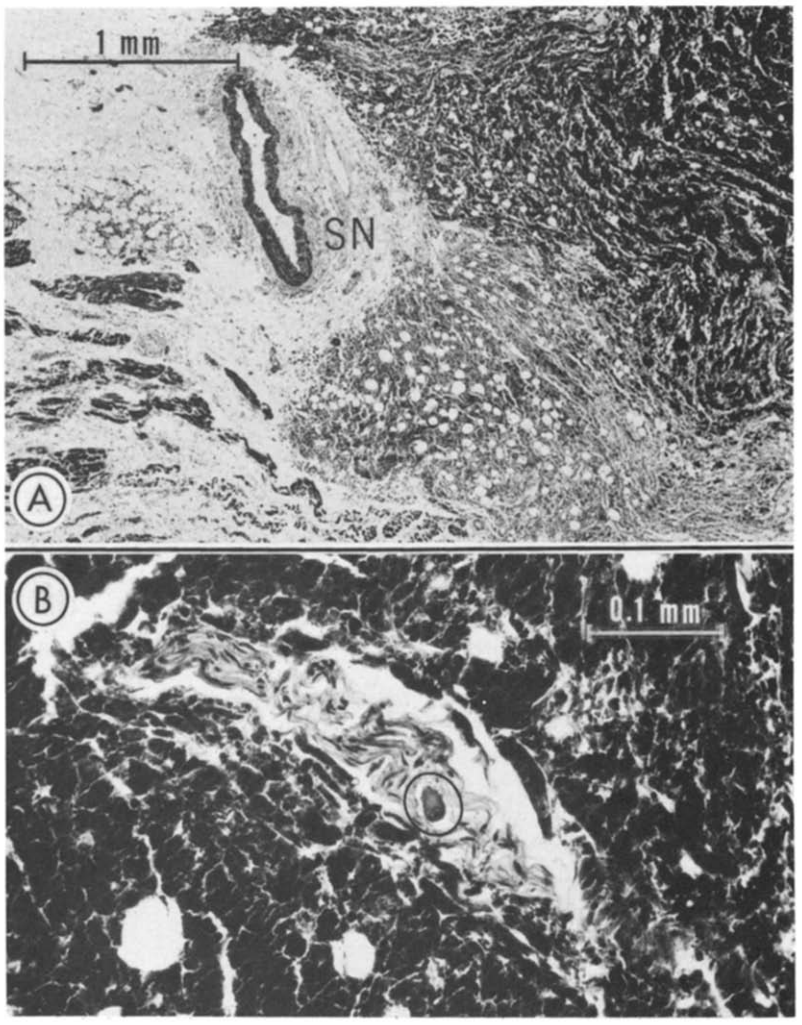


**Figure 17.** In this patient dying with malignant melanoma and cardiac arrhythmias, the sinus node (SN) was virtually obliterated by tumor shown in **A**. A small nerve with a ganglion cell (**circled**) is seen in a sea of tumor cells in **B**.

permanent loss of function. With some histologic examples of minor cardioneural injury, it is likely that function would only be minimally and temporarily impaired. Even with more extensive neural damage or total denervation of the heart (transplantation), it may be anticipated that recovery and reinnervation occur, although their progress is apt to be erratic and inhomogeneous. Given that symmetry and balance of autonomic neural control of the heart are as important as the simple presence of such influence, one must be concerned that uneven recovery of neural influence could be more harmful than no neural influence at all. Inhomogeneity or asymmetry are normally present to some extent, but when these become magnified, they can themselves be the basis for dangerous electrical instability of the heart. Considered thus, recovery from cardioneuropathy could be a mixed blessing.

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